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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,279	07/23/2004	Hideki Endoh	Q82704	2122

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2100 PENNSYLVANIA AVE. NW
WASHINGTON, DC 20037-3213

EXAMINER	
STEELE, AMBER D	
ART UNIT	PAPER NUMBER
1639	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,279	ENDOH ET AL.	
	Examiner	Art Unit	
	Amber D. Steele	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/1/06; 11/13/06*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendment to the claims received on December 1, 2006 canceled claims 1-19 and added new claims 20-23.

Claims 20-23 are currently pending and under consideration.

Priority

2. The present application claims status as a national stage (371) of PCT/JP03/00546 and foreign priority to Japanese applications JP 2002-13721 and JP 2002-257703.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on December 1, 2006 and November 13, 2006 are being considered by the examiner.

Withdrawn Objections

4. The objection to the drawings regarding the description of Figures 1A, 1B, 1C, 6A, and 6B is withdrawn in view of the amendments to the specification received on December 1, 2006.

5. The objection to the abstract regarding length is withdrawn in view of the amendments to the abstract received on December 1, 2006.

6. The objection to claims 17-18 is withdrawn due to the cancellation of the claims in the amendment to the claims received on December 1, 2006.

New Objections Necessitated by Amendment and/or Response

Drawings

7. The drawings are objected to because on page 2 of the Declaration applicants state that "Fig. 9 was incorrectly labeled as representing the ratio of the luciferase activity divided by the β-galactosidase activity...in fact, Fig. 9 contains the raw data, i.e., the luciferase activity without being normalized by the β-galactosidase activity". Therefore, Figure 9 and any other figures which are mislabeled should be corrected. However, applicants also submitted Fig.9' (i.e. Figure 9 prime) with the declaration therefore it is unclear if the applicants are referring to Figure 9 of the specification or Figure 9' of the declaration. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not

accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

8. Claims 20 is objected to because of the following informalities: the common, art recognized name for FLJ13111 is CENPT or CENP-T.

9. Claim 22 is objected to because of the following informalities: chloramphenicol is misspelled (i.e. cloramphenicol). Appropriate correction is required.

Withdrawn Rejections

10. The rejection of claims 17-18 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn due to the cancellation of the claims in the amendment to the claims received on December 1, 2006.

11. The rejection of claims 17-18 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn due to the cancellation of the claims in the amendment to the claims received on December 1, 2006.

12. The rejection of claims 17-18 under 35 U.S.C. 103(a) as being unpatentable over Doebber et al. U.S. Patent 5,847, 008 issued December 8, 1998 and Shimkets and Leach WO

00/58473 published October 5, 2000 is withdrawn due to the cancellation of the claims in the amendment to the claims received on December 1, 2006.

13. The rejection of claims 17-18 under 35 U.S.C. 103(a) as being unpatentable over Taniguchi and Mizukami EP 1 057 896 A1 published December 6, 2000 (published March 3, 1999 as WO 99/10532) and Shimkets and Leach WO 00/58473 published October 5, 2000 is withdrawn due to the cancellation of the claims in the amendment to the claims received on December 1, 2006.

New Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 20-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **written** description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 20 is drawn to a method for screening a drug that increases gene expression from the promoter of the gene for FLJ13111 comprising (a) contacting a test substance with a cell harboring a reporter gene operably linked to the FLJ13111 gene promoter, wherein said promoter

comprises the nucleotide sequence of SEQ ID NO: 26, (b) measuring a change in expression of said reporter gene due to the presence of said test compound, and (c) identifying a compound that increases the expression of said reporter gene. Although addressing a specific sequence of SEQ ID NO: 26, the method states that SEQ ID NO: 26 is the promoter for FLJ13111 and that the change in gene expression is due to the promoter of SEQ ID NO: 26. Therefore, in order for one of ordinary skill in the art to conclude that the applicants had possession of the presently claimed method, SEQ ID NO: 26 must contain the functional promoter (e.g. actual promoter comprising at least the core promoter and may include the proximal or distal promoter regions, enhancers, silencers, intervening regions, etc.) of FLJ13111 (i.e. CENP-T). In addition, the specification states that the promoter sequence for FLJ13111 is unknown and that SEQ ID NO: 26 contains part of the **coding** sequence for FLJ13111 gene at the 3' terminus, but does not provide definitive evidence that SEQ ID NO: 26 contains the promoter region responsible for transcription of the FLJ13111 gene (please refer to pages 100-101) or state how much of the coding sequence is present in the 1870 bp sequence of SEQ ID NO: 26. For example, a TATA box (i.e. TATAAA sequence) that is found in most eukaryotic promoters (please refer to Levine et al. Nature 424: 147-151, 2003) and the CCAAT box (i.e. binding sequence for C/EBP transcription factor) that was found in the CENP-C promoter (please refer to Figure 3 of Poppe et al. Biotechniques 26: 718-726, 1999) are not present in SEQ ID NO: 26.

The resulting data utilizing the Promega pGL3 luciferase reporter vector (Figure 9; Example 14) show that SEQ ID NO: 26 induces a very low level of luciferase activity relative to β-galactosidase activity (e.g. utilized as a transfection control) which is more in line with the amount of activity observed with either a downstream enhancer sequence or background caused

by intervening sequences between the transcription start site and the translation start site than to the amount expected of a transcription promoter that should cause a significant increase in luciferase expression relative to β-galactosidase expression (e.g. applicants show a 1.5 fold increase in luciferase activity relative to β-galactosidase in Figure 9 of the present specification; pGL3 vector utilized). For example, please refer to (A) Chiba-Falek et al. Human Molecular Genetics 10(26): 3101-3109, 2001 Figure 2 wherein the vector pASP-1.46 (i.e. pGL3 with insert) with only sequence prior to the transcription start site had 2-5 fold luciferase expression and the pASP-1.9 vector (i.e. pGL3 with insert) with the promoter region had 16-32 fold luciferase expression, (B) Corti et al. Biochemical and Biophysical Research Communications 286: 381-387, 2001 Figure 2 wherein the vector (i.e. pGL3 with insert) without one TATA box, the CCAAT box, or the Sp1 site therefore not the entire promoter region had 2-6 fold luciferase expression and the vector (i.e. pGL3 with insert) with the entire promoter sequence had 10-41 fold luciferase expression, (C) Bakhshi et al. Gene 275: 93-101, 2001 Figure 3 wherein vectors (i.e. pGL3 with insert) without the CCAAT box or only part of the CCAAT box had 5-10 fold luciferase expression and vectors (i.e. pGL3 with insert) with the entire CCAAT box and other transcription factor binding sites had 18-60 fold luciferase expression, (D) Liu et al. Endocrinology 142(9): 3987-3995, 2001 utilizes the pGL2 vector system which the Promega technical bulletin points out has 20-70% less luciferase expression than pGL3 (please refer to Promega technical bulletin) however vectors comprising the promoter regions have between 4 and 12 fold luciferase expression, (E) Masumoto et al. Gene 291: 169-176, 2002 Figures 1 and 2 show 12-45 fold luciferase expression in vectors (i.e. pGL3 with insert) with the promoter, (F) Tzeng et al. Biochemical and Biophysical Research Communications 291: 270-277, 2002

Figures 2-3 wherein the pGL3-Basic vector = 1 fold relative luciferase expression (e.g. baseline), vectors (i.e. pGL3-Basic with insert) containing only SP1 binding sites and not the entire promoter region have between 2.9-13.2 fold luciferase expression, and vectors with the entire promoter region or the majority of the promoter region have between 35-80 fold luciferase expression, and (G) Liang et al. Gene 282: 75-86, 2002 Figures 3-4 wherein the % of relative luciferase expression is 1-10% for pGL3 Basic empty vector and 100% for vectors (i.e. pGL3 Basic with insert) with the promoter. Please note that all results are relative to transcription controls including β-galactosidase for some references and/or compared to empty vectors. Furthermore, the Promega website suggests that utilization of COS cells (e.g. the same cells utilized in present example 14 and Figure 9) produce even higher levels of luciferase expression than other cells (please refer to Promega technical bulletin and product information for pGL3). Therefore, if SEQ ID NO: 26 contains the promoter for CENPT, higher levels of luciferase expression relative to β-galactosidase would be expected particularly in COS cells.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was *in possession of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See page 1116.).

Thus, the skilled artisan cannot envision the method of claim 20 wherein SEQ ID NO: 26 is definitively the entire promoter region or even the majority of the promoter region for FLJ13111 and would not conclude that any drug that would increase luciferase expression from a

vector containing SEQ ID NO: 26 would significantly alter FLJ13111 expression. While applicants have shown in Figure 9 and Example 14 a slight correlation between PPARγ and SEQ ID NO: 26, applicants have not adequately described SEQ ID NO: 26 so that one of skill in the art would conclude that SEQ ID NO: 26 is the promoter for FLJ13111 (i.e. CENPT; e.g. one of skill in the art **may** conclude that SEQ ID NO: 26 contains a PPARγ binding site wherein pioglitazone may stabilize the interaction, initiate recruitment of other coactivators, etc.). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class wherein the specification provided only the bovine sequence.

16. Claims 20-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **enablement** requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to:

1. The breadth of the claims;
2. The nature of the invention;

3. The state of the prior art;

4. The level of skill in the art;

5. The level of predictability in the art;

6. The amount of direction provided by the inventor;

7. The presence or absence of working examples;

8. The quantity of experimentation necessary needed to make or use the invention based on the disclosure.

See *In re Wands* USPQ 2d 1400 (CAFC 1988):

The breadth of the claims and the nature of the invention:

Although addressing a specific sequence of SEQ ID NO: 26, the method states that SEQ ID NO: 26 is the promoter for FLJ13111 and that the change in gene expression is due to the promoter of SEQ ID NO: 26. Therefore, in order for one of ordinary skill in the art to conclude that the method of the presently claimed invention is enabled SEQ ID NO: 26 must contain the functional promoter (e.g. actual promoter comprising at least the core promoter and may include the proximal or distal promoter regions, enhancers, silencers, intervening regions, etc.) of FLJ13111 (i.e. CENP-T). In addition, the specification states that the promoter sequence for FLJ13111 is unknown and that SEQ ID NO: 26 contains part of the **coding** sequence for FLJ13111 gene at the 3' terminus, but does not provide definitive evidence that SEQ ID NO: 26 contains the promoter region responsible for transcription of the FLJ13111 gene (please refer to pages 100-101) or state how much of the coding sequence is present in the 1870 bp sequence of SEQ ID NO: 26. For example, a TATA box (i.e. TATAAA sequence) that is found in most eukaryotic promoters (please refer to Levine et al. Nature 424: 147-151, 2003) and the CCAAT

box (i.e. binding sequence for C/EBP transcription factor) that was found in the CENP-C promoter (please refer to Figure 3 of Poppe et al. Biotechniques 26: 718-726, 1999) are not present in SEQ ID NO: 26. Applicants have not presented adequate evidence so that one of skill in the art would conclude that SEQ ID NO: 26 is the promoter for FLJ13111 (i.e. CENPT) thus one of skill in the art would not conclude that performing the method as presently claimed would lead to a significant change in CENPT expression. Applicants have shown in Figure 9 and Example 14 a slight correlation between PPARγ and SEQ ID NO: 26 therefore one of skill in the art **may** conclude that SEQ ID NO: 26 contains a PPARγ binding site wherein pioglitazone may stabilize the interaction of PPARγ and the binding site, recruit coactivators, etc. In addition, other potential transcription factor binding sites within SEQ ID NO: 26 have not been determined therefore the breadth of the presently claimed method is difficult to determine (e.g. a change in luciferase expression could be due to various transcription factor binding sites or other factors that may be present in SEQ ID NO: 26; SEQ ID NO: 26 could contain gene expression silencers which are altering the results; SEQ ID NO: 26 could contain nonfunctional regions within the area between the transcription start site and the translation start site, etc.). Accordingly, the claims encompass a vast screening method of all factors that could alter any transcription factor, signaling molecule, or any other factor that potentially alters the activity of SEQ ID NO: 26 to the extent that pioglitazone altered luciferase activity (i.e. from 1.5 fold to 2.5 fold).

The state of the prior art and the level of predictability in the art:

The specification states that the promoter sequence for FLJ13111 is unknown and that SEQ ID NO: 26 contains part of the **coding** sequence for FLJ13111 gene at the 3' terminus, but does not provide definitive evidence that SEQ ID NO: 26 contains the promoter region

responsible for transcription of the FLJ13111 gene (please refer to pages 100-101) or state how much of the coding sequence is present in the 1870 bp sequence of SEQ ID NO: 26. For example, a TATA box (i.e. TATAAA sequence) that is found in most eukaryotic promoters (please refer to Levine et al. Nature 424: 147-151, 2003) and the CCAAT box (i.e. binding sequence for C/EBP transcription factor) that was found in the CENP-C promoter (please refer to Figure 3 of Poppe et al. Biotechniques 26: 718-726, 1999) are not present in SEQ ID NO: 26. In addition, Poppe et al. also teach the unpredictability of determining the human promoter regions for other members of the CENP family (i.e. CENP-C). Therefore, very little is known about the promoter regions of the CENP family, particularly CENPT (e.g. no information), and determining the promoter region requires analysis of deletion constructs with pGL2 or pGL3 reporters, anchored PCR, PCR-mediated genome walking, sequence tagged site assays, genome mapping with various programs, etc. without guaranteed success (i.e. success is unpredictable; please refer to Poppe et al.; Chiba-Falek et al. Human Molecular Genetics 10(26): 3101-3109, 2001; Corti et al. Biochemical and Biophysical Research Communications 286: 381-387, 2001; Bakhshi et al. Gene 275: 93-101, 2001; Liu et al. Endocrinology 142(9): 3987-3995, 2001; Masumoto et al. Gene 291: 169-176, 2002; Tzeng et al. Biochemical and Biophysical Research Communications 291: 270-277, 2002).

The level of skill in the art:

The level of skill would be high, most likely at the Ph.D. level.

The amount of direction provided by the inventor and the existence of working examples:

Regarding the results presented in the specification utilizing the Promega pGL3 luciferase reporter vector (Figure 9; Example 14) to determine if SEQ ID NO: 26 is the CENPT

promoter, Figure 9 shows that pGL3-SEQ ID NO: 26 induces a very low level of luciferase activity relative to β-galactosidase activity (e.g. utilized as a transfection control) which is more in line with the amount of activity observed with either a downstream enhancer sequence alone or background caused by intervening sequences between the transcription start site and the translation start site than to the amount expected of a transcription promoter that should cause a significant increase in luciferase expression relative to β-galactosidase expression (e.g. applicants show a 1.5 fold increase in luciferase activity relative to β-galactosidase in Figure 9 of the present specification). For example, please refer to (A) Chiba-Falek et al. Human Molecular Genetics 10(26): 3101-3109, 2001 Figure 2 wherein the vector pASP-1.46 (i.e. pGL3 with an insert) with only sequence prior to the transcription start site had 2-5 fold luciferase expression and the pASP-1.9 vector (i.e. pGL3 with an insert) with the promoter region had 16-32 fold luciferase expression, (B) Corti et al. Biochemical and Biophysical Research Communications 286: 381-387, 2001 Figure 2 wherein the vector (i.e. pGL3 with an insert) that does not have one of the TATA boxes, the CCAAT box, or the Sp1 site therefore not the entire promoter region had 2-6 fold luciferase expression and the vector (i.e. pGL3 with an insert) with the entire promoter sequence had 10-41 fold luciferase expression, (C) Bakhshi et al. Gene 275: 93-101, 2001 Figure 3 wherein vectors (i.e. pGL3 with an insert) without the CCAAT box or only part of the CCAAT box had 5-10 fold luciferase expression and vectors (i.e. pGL3 with an insert) with the entire CCAAT box and other transcription factor binding sites had 18-60 fold luciferase expression, (D) Liu et al. Endocrinology 142(9): 3987-3995, 2001 utilizes the pGL2 vector system which the Promega technical bulletin points out has 20-70% less luciferase expression than pGL3 (please refer to Promega technical bulletin) however vectors comprising the promoter regions have

between 4 and 12 fold luciferase expression, (E) Masumoto et al. Gene 291: 169-176, 2002 Figures 1 and 2 show 12-45 fold luciferase expression in vectors (i.e. pGL3 with an insert) with the promoter, (F) Tzeng et al. Biochemical and Biophysical Research Communications 291: 270-277, 2002 Figures 2-3 wherein the pGL3-Basic vector = 1 fold relative luciferase expression (e.g. baseline), vectors (i.e. pGL3-Basic with an insert) containing only SP1 binding sites and not the entire promoter region have between 2.9-13.2 fold luciferase expression, and vectors (i.e. pGL3-Basic with an insert) with the entire promoter region or the majority of the promoter region have between 35-80 fold luciferase expression, and (G) Liang et al. Gene 282: 75-86, 2002 Figures 3-4 wherein the % of relative luciferase expression is 1-10% for pGL3 Basic empty vector and 100% for vectors (i.e. pGL3 Basic with an insert) with the promoter. Please note that all results are relative to transcription controls including β-galactosidase for some references and/or compared to empty vectors. Furthermore, the Promega website suggests that utilization of COS cells (e.g. the same cells utilized in present example 14 and Figure 9) produce even higher levels of luciferase expression than other cells (please refer to Promega technical bulletin and product information for pGL3). Therefore, if SEQ ID NO: 26 contains the promoter for CENPT, higher levels of luciferase expression relative to β-galactosidase would be expected particularly in COS cells. Moreover, a detailed analysis of SEQ ID NO: 26 is not provided therefore potential transcriptional factor binding sites present in the sequence are not known. While, the applicants have shown that a slight increase (e.g. from 1.5 fold to 2.5 fold) in luciferase expression occurs in the presence of pioglitazone (e.g. PPAR ligand), this does not definitively show that SEQ ID NO: 26 is the promoter for CENPT. One of skill in the art **may** conclude that SEQ ID NO: 26 contains a PPARγ binding site (e.g. wherein pioglitazone stabilizes the interaction of PPAR and

the binding site, recruits coactivators, etc.), however an analysis of SEQ ID NO: 26 for potential binding sites has not been performed.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

In light of the unpredictability surrounding the claimed subject matter, the undue breadth of the claimed invention's intended use, and the lack of adequate guidance to practice the presently claimed invention one of skill in the art would be unable to perform the presently claimed method without engaging in undue experimentation. Please note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991). In this case, Applicants have not provided sufficient working examples that would lead one of skill in the art to conclude that SEQ ID NO; 26 is the promoter for CENPT. Thus, a change in expression due to a drug screened in the presently claimed method cannot be attributed to SEQ ID NO: 26 being the promoter for CENPT. Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed (e.g. detailed analysis of the sequence via deletion constructs with pGL2 or pGL3 reporters, anchored PCR, PCR-mediated genome walking, sequence tagged site assays, genome mapping with various programs, etc. without guaranteed success in determining that SEQ ID NO: 26 contains the promoter for CENPT; please refer to Poppe et al.; Chiba-Falek et al. Human Molecular Genetics 10(26): 3101-3109, 2001; Corti et al. Biochemical and Biophysical Research Communications 286: 381-387, 2001; Bakhshi et al. Gene 275: 93-101, 2001; Liu et al. Endocrinology 142(9): 3987-3995,

2001; Masumoto et al. Gene 291: 169-176, 2002; Tzeng et al. Biochemical and Biophysical Research Communications 291: 270-277, 2002). Thus, due to the inadequacies of the instant disclosure one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Therefore based on the evidences as a whole regarding each of the above factors, the specification, at the time the application was filed, does not satisfy the enablement requirement for the instant claimed method of screening a drug comprising: (a) contacting a test substance with a cell harboring a reporter gene operably linked to the FLJ13111 gene promoter, wherein said promoter comprises the nucleotide sequence of SEQ ID NO: 26, (b) measuring a change in expression of said reporter gene due to the presence of said test compound, and (c) identifying a compound that increases the expression of said reporter gene.

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 20-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants assert that SEQ ID NO: 26 is the promoter for FLJ13111 and that the change in gene expression of the present method is due to the promoter of SEQ ID NO: 26. However, the specification states that the promoter sequence for FLJ13111 is unknown and that SEQ ID NO: 26 contains part of the **coding** sequence for FLJ13111 gene at the 3' terminus, but does not provide definitive evidence that SEQ ID NO: 26 contains the promoter region responsible for transcription of the FLJ13111 gene (please refer to pages 100-101) or state how

much of the coding sequence is present in the 1870 bp sequence of SEQ ID NO: 26. For example, how much of the 3' terminus of the 1870 bp sequence of SEQ ID NO: 26 is actually the coding sequence? Where exactly is the promoter sequence in the 1870 bp sequence of SEQ ID NO: 26? Is a PPARγ binding site present in SEQ ID NO: 26? Does SEQ ID NO: 26 contain the entire promoter region for CENPT? Does SEQ ID NO; 26 contain a portion of the promoter region and if so which portion? What transcription factor binding sites does SEQ ID NO: 26 contain?

Response to Amendment

19. The declaration under 37 CFR 1.132 filed December 1, 2006 has been entered and considered. However, the declaration is moot due to the cancellation of claims 17-18. Please refer to the new rejections for claims 20-23. In addition, the declaration refers to certain issues that are also present in the new rejections of claims 20-23, therefore, the declaration is also insufficient to overcome the rejections of claims 20-23 (see above) because: Applicants contend that (a) Figure 9 is mislabeled and actually contains raw data, (b) SEQ ID NO: 26 has a promoter for FLJ13111, (c) Figure 9 shows that the reporter vector comprising SEQ ID NO: 26 has 29 times higher luciferase induction compared to the pGL3 vector without SEQ ID NO: 26, (d) it is not common in the field of reporter assay to use a known reporter for control, (e) luciferase activity differs depending on the retaining time of the vector in cells, types of cell, conditions of measurement apparatus, etc. In response, the examiner contends that (a) it is unclear if Figure 9 or Figure 9' (i.e. supplemental figure provided with the declaration) contains raw data, (b) applicants have not definitively shown that SEQ ID NO: 26 is the promoter for CENPT, contains

a PPARγ binding site, contains any transcription factor binding sites, contains a RNA polymerase binding site, etc. (c) the results from the Promega website show that the pGL3 vector with enhancer elements (e.g. pGL3 enhancer vector commercially available from Promega) can have approximately 34.5 times higher luciferase activity than the pGL3 basic (please refer to Figure 7 of the Promega technical bulletin wherein pGL3 basic has 0.54 relative light units and pGL3 enhancer has 18.765 relative light units based on the 1350 relative light units from the pGL3 control vector), (d) Promega has a commercially available pGL3 control vector for utilization with the pGL3 system (please refer to Promega catalogue number E1741), and (e) while the examiner agrees that luciferase activity differs between cell types (please refer to Groskreutz et al. Promega Notes Magazine 50, 1995 particularly Figures 2 and 3) Promega explicitly states that COS cells (i.e. the same cells utilized by applicants) may have higher expression of the reporter gene compared to other cells due to the SV40 large T antigen that promotes replication from the SV40 origin found in the pGL3 vectors (please refer to Promega notes section for pGL3 vectors). Regarding the various references cited:

A. Chiba-Falek et al. (Human Molecular Genetics 10(26): 3101-3109, 2001) utilized 293T and SH-SY5Y cells, deletion constructs, a control plasmid containing only sequences downstream of the transcriptional start site, a control pGL3 empty vector, a pRL-TK plasmid as a transfection control, a pRL-SV40 vector as a reference (e.g. contains the SV40 early enhancer/promoter region) to characterize a promoter and enhancer region and do not provide raw data (thus a comparison of luciferase activity can not be made; Figure 2 shows 3-60 fold luciferase expression which is greater than the 1.5 fold increase of present Figure 9; see above for a more detailed analysis).

B. Corti et al. (Biochemical and Biophysical Research Communications 286: 381-387, 2001) utilized Cos-7, U178-MG, SKN-MC cells, deletion constructs, pRL-RSV was utilized to normalize for transfection efficiency, pGL3 empty vector as a control, and pGEM-4Z was utilized as a background control to characterize a promoter and enhancer region and do not provide raw data (thus a comparison of luciferase activity can not be made; Figure 2 shows 5-45 fold luciferase expression which is greater than the 1.5 fold increase of present Figure 9; see above for a more detailed analysis).

C. Bakhshi et al. (Gene 275: 93-101, 2001) utilized U87MG cells, deletion constructs, pCMV-β-gal as to normalize for transfection, a control pGL3 empty vector to characterize a promoter and enhancer region and do not provide raw data (thus a comparison of luciferase activity can not be made; Figure 3 shows 10-60 fold luciferase expression which is greater than the 1.5 fold increase of present Figure 9; see above for a more detailed analysis).

D. Liu et al. (Endocrinology 142(9): 3987-3995, 2001) utilized MC3T3-E1 cells, Cos-7 cells which produced higher β-gal activity than other cells, deletion constructs, pGL2 empty vector as a control, deletion constructs, pSV β-gal as a normalization control for transfection to characterize a promoter and enhancer region and do not provide raw data (thus a comparison of luciferase activity can not be made; Figures 4-5 show 2-12 fold luciferase expression with pGL2 vector that has 20-70 fold less luciferase expression than pGL3 which is greater than the 1.5 fold increase of present Figure 9 utilizing pGL3; see above for a more detailed analysis).

E. Masumoto et al. (Gene 291: 169-176, 2002) utilized deletion constructs, NIH3T3 cells, pCH110 was utilized to normalize for transfection, empty pGL3 vector to characterize a

promoter and enhancer region and do not provide raw data (thus a comparison of luciferase activity can not be made; Figures 1-2 show 5-60 fold luciferase expression which is greater than the 1.5 fold increase of present Figure 9; see above for a more detailed analysis).

F. Tzeng et al. (Biochemical and biophysical Research Communications 291: 270-277, 2002) utilized deletion constructs, pGL3 empty vector as a control, IEC-8 cells, pRL-TK as a transfection control to characterize a promoter and enhancer region and do not provide raw data (thus a comparison of luciferase activity can not be made; Figures 2-3 show 20-120 fold luciferase expression which is greater than the 1.5 fold increase of present Figure 9; see above for a more detailed analysis).

G. Liang et al. (Gene 282: 75-86, 2002) utilized deletion constructs, THP-1 and Raw264.7 cells, pRL-TK as a transfection control, pGL3 empty vector, maximal activity control (i.e. EMMPRIN promoter) to characterize a promoter and enhancer region and do not provide raw data (thus a comparison of luciferase activity can not be made; Figures 3-4 and 6-7 show 60-100% of maximum luciferase expression and 50-400 fold luciferase expression which is greater than the 1.5 fold increase of present Figure 9; see above for a more detailed analysis).

Thus, the above-mentioned references utilize deletion constructs to determine the exact location of the promoter and/or enhancer elements, provide a detailed map of the location of the various transcription regulation elements within the sequence, and may utilize computational analysis of the sequences to determine various known sequences important in transcriptional regulation.

Conclusion

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ADS
February 26, 2007

MARK L. SHIBUYA
PRIMARY EXAMINER